REMARKS/ARGUMENTS

Claims status

Claims 1-79 are pending in this application. Claims 14, 15, 19, 78 and 79 are withdrawn from consideration as being drawn to a nonelected Group or Species. The claims currently under consideration are 1-13, 16-18, and 20-77.

Amendments to the claims

Claims 1, 58, 63, and 73 have been amended to recite storing the genotype "in a medium accessible to a user". This amendment is fully supported in the specification; for example on pages 40-41 and in Figures 4-6. Applicants respectfully request entry of the claims as amended.

The invention

The present invention provides methods, apparatus and computer program code for determining the genotype of one or more individuals. The methods of the invention use at least one measure of the amount of an allele of one or more genetic markers; this measure of the amount of an allele is used in statistical methods described in the present application to determine the genotype of the one or more individuals.

35 U.S.C. §101 rejection

Claims 1-13, 16-18, and 20-77 are rejected under 35 U.S.C. §101 as being directed to non-statutory subject matter. The Examiner states that the instant claims are drawn to a genetic algorithm and that a genetic algorithm is non-statutory unless the claims include a step of physical transformation, or if the claims include a useful, tangible and concrete result. *Office Action, page 2.* The Examiner further states that this rejection "could be overcome by amendment of the claims to recite that a result of the method is outputted to a user, a display, a memory, or a computer on a network, or by including a physical transformation. *Office Action, page 3.*

The rejection on this basis is believed to be obviated by the amendment to the claims herein. Initially, Applicants respectfully submit that the instant invention is not limited to a

"genetic algorithm" as characterized by the Examiner, but instead encompasses methods and computer system used in the process of identifying the genotype of one or more individuals. Applicants also respectfully submit that the instantly claimed invention clearly provides a useful, concrete and tangible result. In particular, the process of identifying the genotype of one or more individuals is of particular applicability in the field of molecular biology, as well as all of its research and industrial applications. Identification of the genotype is itself a tangible result, because it represents aspects of the genetic code of the individual, which is not an abstract idea but a tangible physical quality.

Notwithstanding the foregoing, and in the interest of advancing the prosecution of this application, Applicants have adopted an amendment to the claims which clarifies that the genotypes identified by the claimed methods are stored in a user-accessible medium. Thus, while Applicants believe that the claims as originally presented clearly provided a tangible, useful and concrete result, it is believed that the amendment to the claims further clarifies the tangible, useful and concrete nature of the result of the claims. The amendments are fully supported by the specification, for example on page 40, paragraph [00124] ("computer readable media"); page 41, paragraph [00128] ("video displays"; "touch-sensitive displays"; "network interface" which receives "information from the network" or might "output information to the network"); page 19, paragraph [0068] ("stored intensity data"), page 21, paragraph [0074] ("relational database"), page 24, paragraph [0081] ("The process 402 writes the genotyping results data to three other tables"), page 24, paragraph [0082] ("An assigned_genotype data item represents the genotype assigned to a particular cluster."), page 26, paragraph [0088] ("the corresponding data items are kept in memory with the final results being written to database"), and Figures 4-6.

Applicants respectfully submit that the claims as amended fulfill the requirements under 35 U.S.C. §101 for patentable subject matter and respectfully request that the rejection on this basis be withdrawn.

Prior 35 U.S.C. §112 rejection

Applicants gratefully acknowledge withdrawal of this rejection.

Prior 35 U.S.C. §103 rejections

Applicants gratefully acknowledge withdrawal of the previous §103 rejections.

Current 35 U.S.C. §103 rejections

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must not based on applicant's disclosure. See MPEP 2142 (citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)).

The Supreme Court recently affirmed the obviousness analysis that it had set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), and the Court also stated that "[t]here is no necessary inconsistency between the idea underlying the TSM [i.e., teaching-suggestion-motivation] test and the *Graham* analysis." *KSR Int'l Co. v. Teleflex Inc.*, No. 04-1350, slip op. at 13 (2007). Thus, the Supreme Court has not invalidated the TSM test, but rather only rejected its "rigid" application. *See id.* at 11. An obviousness rejection continues to require articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *See id.* at 14 (citing *In re Kahn*, 411 F.3d 977, 988 (Fed. Cir. 2006)). The continued importance of the TSM elements is further supported in the May 3, 2007 memorandum from Margaret A. Focarino to the USPTO Technology Center directors, which stated: "***in formulating a rejection under 35 U.S.C. §103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.***"

Applicants respectfully submit that each of the criteria set forth above have not been satisfied by any of the combinations of references cited by the Examiner, and thus, a *prima facie*

case of obviousness has not been established. Applicants' respectfully traverse all of the §103 rejections cited in the Office Action for the reasons set forth below.

Lee et al ("Lee")

Claims 1-2, 5-7, 63 and 73 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lee. Applicants respectfully disagree.

Lee is concerned with evaluating gene expression data in such a way as to be able to compare results from different experiments. Lee's goal is to separate true biologic variability between expression of particular genes in different cell lines from experimental variability associated with instrumentation, labeling, and scanning. See for example the last full paragraph on page 229: "In this estimation procedure we especially want to decompose the total variability into several biological and experimental components, so that we can evaluate the significance of such biological interaction effects purely based on biological variability, removing that of experimental variability." Thus, using algorithms outlined on pages 230-231, Lee allows the creation of normalized data that can be compared within experiments to determine the reliability of the data. The values reported in Tables 1 and 2 are normalized score, "Nscores", which as defined on page 232, "can be interpreted as the ratio of each interaction effect and its corresponding sample standard error, which will directly represent the statistical significance of the effects of each combination of the biological factors". Lee et al. thus provides a relational study of gene expression in which genes derived from a particular cell line are assigned a relative score, reflecting the statistical significance of different levels of gene expression.

However, Lee points out that "[h]owever, owing to the design of the 60 cell line data, the cancer relevant and general cell origin gene factors are confounded for the genes with high interaction effects in this application. In fact, there may be more genes relevant to specific origin of cell lines rather that [*sic.*] cancer relevant ones, so that the genes identified with high interaction effects may not directly lead us to discovery of genes responsible for cancer...." *Lee, pages 232-233.* Thus, as further discussed below, Lee does not, contrary to the Examiner's position, teach or suggest that the genes in Tables 1 and 2 are alleles most likely to result in

colon and melanoma cancers. The authors in Lee go out of their way to reiterate that the data is not to be used in this way.

Applicants respectfully submit that Lee fails to teach every element of the instant claims. As the Examiner notes, Lee does not explicitly teach how the information it calculates related to interaction effects could relate to the amount of an allele in each of the 60 cancer-related genes. *Office Action, page 8.* In fact, the calculations in Lee do not provide an amount of an allele at all, but rather show a relational list of genes accompanied by a kind of statistical correlation between genes in a particular experiment. *Lee, page 229.* Lee does not teach the use of "at least one measure of the amount of a given allele" as is recited in the instant claims. Lee also fails to teach "assigning the measure of the amount of the allele to a group" and "assigning a genotype to the group" as is described in the instant application. Lee's study starts with a particular cell type and uses the organ of origin in the calculation of "interaction effects" among the genes expressed by that cell type. Lee provides no further method by which the calculated score is then used to assign the gene of interest to a particular group. Since Lee fails to teach both using a measure of an allele and assigning a measure of an allele to a group, then Lee necessarily fails to teach the claimed method of using a probability clustering process and a distance-based clustering process to assign the measure of a given allele to a group. In addition, Lee does not teach or suggest any method by which the genotype of an individual can be determined using its analysis technique. Lee thus fails to provide every element of the instantly claimed invention and cannot support a *prima facie* case of obviousness.

The Examiner states that Lee uses "hierarchical clustering to measure the expression of 60 different human cancer cell lines." *Office Action, page 8.* Applicants respectfully disagree with this characterization. The only mention of "hierarchieal clustering" in Lee is a reference to another paper by Scherf et al. in which a hierarchical clustering approach was used to determine that a subset of 39 of the 60 cancer cell lines were reliable. *Lee, page 232.* Thus, Lee does not teach the use of hierarchical clustering, and in fact, Lee's results were based on a subset of the cell lines which were themselves chosen based on a hierarchical clustering method conducted in another study. Lee can not be characterized as teaching the use of hierarchical clustering to measure the expression of 60 different human cancer cell lines, because Lee's algorithms are not

hierarchical clustering algorithms. Lee does describe the use of two layers of "hierarchical structure" for determining components of the variance. *Lee, p. 234.* However, these hierarchical structures were not "clustering" methods and were used to calculate the variance, *i.e.*, the error, in the gene expression data. Thus, the methods described in Lee can not be characterized as assigning the measure of the amount of an allele to a group using "one or more of a probability clustering process and a distance-based clustering process" as is recited in the instant claims, because Lee does not provide hierarchical clustering algorithms.

The Examiner states that "Comparison of the score of the individual in question with the scores listed in the tables can indicate the probability of a cancerous allele." *Office Action, page 8.* Applicants respectfully suggest that this is a mischaracterization of Lee. The scores in Lee provide an estimate of the reliability of the data from a particular experiment; the scores in Lee are not indications of probability of the expression of a particular allele. Lee provides relative scores which indicate the interaction between genes, and those calculations of interaction are corrected for experimental error variability. *Lee, page 230.* Thus, these relative scores are not values related to probability, and the score of an individual could not be compared to the scores in the table to indicate probability of a particular allele.

The Examiner states that it would have been obvious for one of ordinary skill to "modify the gene expression profiles of Lee et al. in view of assigning an amount of allele of a given gene to an individual because by comparing the amount of an allele of a gene (i.e. Tables 1 and 2 of Lee et al.), to the scores listed in these tables, one can result in a measure of probability of the existence of alleles likely to result in certain types of cancers." *Office Action, pages 8-9.* Applicants respectfully disagree. As discussed above, Lee does not provide a measure of the amount of an allele of a gene. Furthermore, a study of gene expression correlated with certain types of cancer cell lines is not a method for determining the genotype of an individual. As the Examiner noted, Lee does not suggest using its data to determine the genotype of an individual. Further, contrary to the Examiner's assertion that "A change in the expression level correlates to the variation of the allelic phenotype" (*Office Action, page 8*), changes in expression do not necessarily correlate to a particular allele of the gene being expressed since changes in expression can also be the result of epistatic and/or environmental effects. Therefore, one of

ordinary skill in the art would not use the analysis methods of Lee to determine genotypes because there would be no expectation of success, and therefore no motivation to do so.

In fact, as argued above, Lee states that its methods may not "directly lead us to discovery of genes responsible for cancer". *Lee, pages 232-233.* This statement in Lee teaches away from the claimed method of determining the genotype of an individual based on the amount of an allele. In addition, Lee teaches away from using clustering in the analysis of gene expression data: "We have identified novel genes whose effects have not been revealed by the previous approaches to the gene expression data." *Lee, page 228, abstract, last line.* As the Examiner will appreciate, teaching away from the claimed invention is an indicia of unobviousness. *In re Grasselli, 713 F.2d 731, 743 (Fed. Cir. 1983).*

Furthermore, Applicants respectfully suggest that there is no motivation in Lee for one of skill in the art to even attempt (however unsuccessfully) to determine the genotype of an individual based on the data in Lee. Lee's stated purpose is to provide "good reference lists for various gene expression studies of origin specific cancer." *Lee, page 233.* The only motivation to try to determine genotype based on the data in Lee could only come from the instant specification, which, as the Examiner will appreciate, is an improper use of hindsight. *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998).

Applicants suggest that for at least the reasons provided above, Lee cannot support a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Lee in view of Xue et al., ("Xue")

Claims 1 and 3-4 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lee in view of Xue. Applicants respectfully disagree.

As discussed above, Lee fails to teach all elements of the instantly claimed invention. Xue does not rectify the deficiencies in Lee, because Xue also fails to provide the elements of taking the measure of an allele, assigning that measure to a group, and assigning a genotype to that group based on a property of that group. Thus the combination of the references cannot support a *prima facie* case of obviousness.

Furthermore, there is no motivation to combine Xue and Lee, because the two references involve different kinds of data analysis. Lee uses data from cDNA microarrays to perform a statistical analysis of expression patterns across different cell lines. In contrast, Xue detects single nucleotide polymorphisms by determining the length of reaction products from a chain elongation reaction -- the length of the extension products identifies the SNP nucleotide. Thus, the data in Xue does not provide data that can be used to calculate the "interaction effects" or the "variance components" used in the statistical analysis method of Lee. The methods of Lee can not be used with the "binary" type of information that results from the teachings in Xue (*e.g.*, what base is present at a particular position). A person of skill in the art would not be motivated to take the chain elongation data from Xue to use in the statistical methods of Lee, and there is nothing in either reference that suggests a motivation for such a combination. Similarly, one of skill in the art would have no expectation of success in performing the instant invention upon combining Xue and Lee, because the methods of Lee can not be used with the data resulting from Xue.

The Examiner states that the motivation to combine the teachings of Xue with Lee derives from the purpose of the study of Xue, which is to screen a large number of samples for single nucleotide polymorphisms. However, as discussed above, the data generated by the methods of Xue can not be used in the statistical methods of Lee, and therefore one of skill in the art would not be motivated to combine the teachings of the two references.

Since the combination of Xue and Lee does not support a *prima facie* case of obviousness, Applicants respectfully request that this rejection be withdrawn.

Lee in view of Krishna et al. ("Krishna")

Claims 1, 9-13, 16-18, 20-22, 25, 63, 65, 67-70, 73, 75 and 76 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lee in view of Krishna. Applicants respectfully disagree.

As discussed above, Lee fails to teach all elements of the instantly claimed invention. Krishna does not rectify the deficiencies in Lee, because Krishna also fails to provide the elements of taking the measure of an allele, assigning that measure to a group, and assigning a

genotype to that group based on a property of that group. Krishna teaches a "genetic algorithm", but this "genetic algorithm" is not an algorithm that uses genetic data, but is rather a kind of stochastic algorithm that can be used to organize data into groups. One of skill in the art would not be motivated to combine the teachings of Lee and Krishna, because the two references teach different kinds of algorithms using very different kinds of data.

The combination of the references cannot support a *prima facie* case of obviousness. Applicants therefore respectfully request that this rejection be withdrawn.

Lee in view of Excoffier et al. ("Excoffier")

Claims 1, 8, 63, and 73-74 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lee in view of Excoffier. Applicants respectfully disagree.

As discussed above, Lee fails to teach all elements of the instantly claimed invention. Excoffier does not rectify the deficiencies in Lee, because Excoffier also fails to provide the elements of taking the measure of an allele, assigning that measure to a group, and assigning a genotype to that group based on a property of that group. Thus the combination of the references cannot support a *prima facie* case of obviousness.

The Examiner states that it would have been obvious to one of skill in the art to modify Lee in view of Excoffier, because Excoffier teaches the use of EM algorithms for surveying chromosomes. Applicants respectfully disagree with this characterization, because the references disclose different kinds of algorithms that result in different kinds of results: Lee's algorithms result in a scoring of gene expression that is influenced by the cell of origin and the other genes expressed in that cell, whereas Excoffier's algorithms provide estimates of haplotype frequencies in a large sample. One of skill in the art would not be motivated to combine the teachings of these references. Furthermore, neither reference provides a measure of an allele or a method by which that the measure of the allele is used to assign the allele to a group; in addition, neither reference provides a method of assigning a genotype to a group based on a property of the group. There would thus be no expectation of success of practicing the instantly claimed invention upon combining the teachings of these references. A *prima facie* case of obviousness

cannot be maintained by these references, and Applicants respectfully request that this rejection be withdrawn.

Lee in view of Krishna, Montoya-Delgado et al. ("Montoya-Delgado") and Frey et al. "Frey")

Claims 1, 25-53, 63, 65, 73 and 77 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lee in view of Krishna as applied to claims 1, 9-13, 16-18, 20-22, 25, 63, 65, 67-70, 73, 75 and 76 and further in view of Montoya-Delgado in view of Frey. Applicants respectfully disagree.

As discussed above, the combination of Lee and Krishna cannot support a *prima facie* case of obviousness. Montoya-Delgado in view of Frey do not rectify the deficiencies of Lee and Krishna, because neither Montoya-Delgado nor Frey provide the elements of taking the measure of an allele, assigning that measure to a group, and assigning a genotype to that group based on a property of that group. Thus the combination of the references cannot support a *prima facie* case of obviousness. Applicants therefore respectfully request that this rejection be withdrawn.

Lee in view of Krishna and further in view of Excoffier

Claims 58-62, 63, 67 and 69-72 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lee in view of Krishna as applied to claims 1, 9-13, 16-18, 20-22, 25, 63, 65, 67-70, 73, 75 and 76 and further in view of Excoffier. Applicants respectfully disagree.

As discussed above, Lee and Krishna cannot be combined to provide the instant invention. As also discussed above, Lee and Excoffier cannot be combined to provide the instant invention. Combination of Lee with Krishna and Excoffier also fails to support a *prima facie* case of obviousness, because none of the three references provides the elements of taking the measure of an allele, assigning that measure to a group, and assigning a genotype to that group based on a property of that group. Thus the combination of the references cannot support a *prima facie* case of obviousness. Applicants therefore respectfully request that this rejection be withdrawn.

Lee in view of Krishna further in view of Babu et al. ("Babu")

Claims 63 and 66 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Leein view of Krishna as applied to claims 1, 9-13, 16-18, 20-22, 25, 63, 65, 67-70, 73, 75 and 76 and further in view of Babu. Applicants respectfully disagree.

As discussed above, the combination of Lee and Krishna cannot support a *prima facie* case of obviousness. The combination of Lee and Krishna in view of Babu also cannot support an obviousness rejection, because Babu does not rectify the deficiencies of Lee and Krishna. None of the three references provides the elements of taking the measure of an allele, assigning that measure to a group, and assigning a genotype to that group based on a property of that group. Thus the combination of the references cannot support a *prima facie* case of obviousness. Applicants therefore respectfully request that this rejection be withdrawn.

Lee in view of Krishna in view of Montoya-Delgado in view of Frey and further in view of Babu

Claims 1, 26, 38-39, 44 and 54-57 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lee in view of Krishna in view of Montoya-Delgado in view of Frey as applied to claims 1, 25-53, 63, 65, 73 and 77 and further in view of Babu. Applicants respectfully disagree.

As discussed above, Lee cannot be combined with Krishna or with Montoya-Delgado in view of Frey or with Babu to provide the instant invention. The combination of all five references together does not rectify the deficiencies of the individual combinations, and thus the combined references can not support a *prima facie* case of obviousness. Applicants therefore respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-442-1000.

Respectfully submitted,

Date: July 18, 2007

By: 31,801 for

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